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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,298	12/18/2006	M. Ian Phillips	USF-200TCXZ1	6761

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,298	PHILLIPS ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/06/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/567,298 is a 371 of PCT/US04/26195 filed on 08/11/2004 which claims benefit of 60/494,184 filed on 08/11/2003, and claims benefit of 60/494,185 filed on 08/11/2003, and claims benefit of 60/513,067 filed on 10/21/2003, and claims benefit of 60/513,657 filed on10/23/2003.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-20, drawn to drawn to a genetically modified cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product, in the reply filed on 11/14/2008 is acknowledged. Applicants further elected heme oxygenase-1 (HO-1) as the single therapeutic product from claim 7, mesenchymal stem cell (MSC) as the single cell from claim 13, cardiac cell as the single cell from claim 14, and hypoxia as the single physiological stimulus from claim 19. Applicants noted that the elected species for claims 14 and 19 have been added to the claims by the Preliminary Amendment that accompanies the election.

With regard to the election of hypoxia as the single physiological stimulus from claim 19, it is worth noting that the election of hypoxia as a species reads on the species listed in claim 18 that include hypoxia, glucose, a tumor marker, and an atherosclerosis indicator of inflammation. Furthermore, as hypoxia and glucose are two distinct species of physiological stimuli that lead to distinct physiological responses, the limitation "wherein said physiological stimulus- sensitive

chimeric transactivator comprises a glucose-sensitive element" recited in claim 20 reads on non-elected species glucose. Accordingly, claim 20 is not readable on elected species hypoxia.

Claims 1-27 are pending. Claims 20-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1-19 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 reads as follows: The cell of claim 1, wherein said therapeutic product is a polypeptide that is endogenous to said cell.

Claim 1 reads as follows: A genetically modified cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

It is noted that an endogenous gene/protein is commonly accepted in the art referring to the gene located in the chromosomes of a cell and the protein encoded by the chromosomal gene whereas exogenous gene/polynucleotide commonly refers to a transgene introduced into a cell by an extra-chromosomal vector. Therefore, it is unclear what it is supposed to mean by combination of the recitation of "exogenous polynucleotide" in claim 1 and recitation of "wherein said therapeutic product is a polypeptide that is endogenous to said cell" in claim 17, which depends from claim 1.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

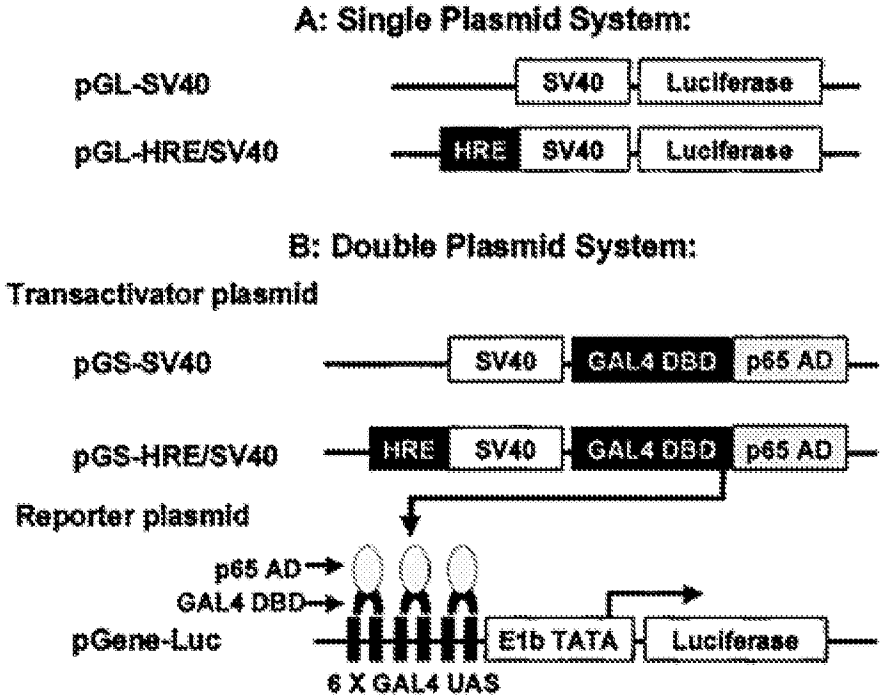
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-9, 11, and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001).

Claim interpretation: The limitation "wherein said therapeutic product is a polypeptide that is endogenous to said cell" recited in claim 17 is interpreted as any therapeutic product that

is a polypeptide encoded by a transgene (i.e. exogenous polynucleotide) and the genome of said cell comprises gene(s) on chromosomes that can encode the same polypeptide (which is considered endogenous to the said cell).

With regard to claims 1-9, 11, and 14-19 of instant application, Tang et al. teaches that coronary artery disease frequently involves repeated bouts of myocardial ischemia, and to automatically up-regulate the cardioprotective transgenes under hypoxic ischemia, a "vigilant vector" gene therapy system was developed and tested in a rat embryonic cardiac myoblast (H9c2, which reads on limitation cardiac cell recited in claim 14 of instant application). Tang et al. teaches that, in the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal. Furthermore, Tang et al. teaches that a novel double plasmid system was designed to elevate the potency of the vigilant vector, and instead of putting the promoter and the reporter gene in the same plasmid (single plasmid system), Tang et al. separated them into two plasmids: the transactivator plasmid and reporter plasmid (double plasmid system). Tang teaches that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain (which reads on the limitations of claim 6 of instant application), and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene (See abstract and Figure 1 shown below, Tang et al., 2002).



It is noted that with regard to the limitation recited in claim 15 "wherein said gene amplification system comprises nucleic acid sequences encoding multiple therapeutic products are the same or different", this limitation reads on over-expression of the same gene resulting from transactivator binding to the UAS (upstream activation sequences) of the gene as taught by Tang et al.

Tang et al. does not teach a nucleic acid sequence encoding a therapeutic product recited in claim 1 and said therapeutic product being heme oxygenase-1 (OH-1) recited in claim 7 of instant application.

Juan et al. teaches the followings: (i) adenovirus-mediated gene transfer of HO-1 (which reads on claim 9 of instant application) in arteries reduces iron overload and inhibits lesion formation in apolipoprotein E (apoE)-deficient mice (See abstract, Juan et al., 2001), and (ii) heme oxygenase (HO) is a rate-limiting enzyme in heme catabolism; one of the isozymes, HO-

1, is a stress-response protein and can be induced by a variety of oxidation-inducing agents, including heme/hemoglobin, heavy metals, UV radiation, cytokines, and others, and induction of HO-1 leads to the degradation of pro-oxidant heme to carbon monoxide (CO) and biliverdin (See introduction, page 1519, Juan et al., 2001).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Tang et al. regarding a genetically modified/transfected cell comprises two plasmids: the transactivator plasmid and reporter plasmid and that that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain, and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene, with the teachings of Juan et al regarding expressing HO-1 gene from an adenoviral vector for therapeutic purpose to arrive at the claimed expression cassette as recited in claims 1-9, 11, and 14-19 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Tang et al. with the teachings of Juan et al. because Tang et al. establishes the double plasmid system sensitive to hypoxia condition for gene therapy of coronary artery disease by monitoring the expression of luciferase as a reporter and Juan teaches Adv-OH-1 construct (which expresses OH-1 from an adenoviral vector) for gene therapy of atherosclerosis since HO-1 is a stress-response protein and can be induced by a variety of oxidation-inducing agents. Furthermore, substitution of a reporter gene with a gene encoding a therapeutic protein in the context of a

vector, either a plasmid or a viral vector, is a common practice in molecular biology depending on the gene of interest to be expressed.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoplast cell line by the teachings of Tang et al., and (ii) the transfection and expression of Adv-OH-1 construct (which expresses OH-1 from an adenoviral vector) for gene therapy of atherosclerosis by the teachings of Juan et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

3. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001), as applied to claims 1-9, 11, and 14-19 above, and further in view of **Nicklin et al.** (Nicklin et al., Tropism-modified adenoviral and adeno-associated viral vectors for gene therapy, *Curr Gene Ther.* 2(3):273-93, 2002).

The teachings of Tang et al. and Juan et al. have been discussed in the preceding section of the rejection of claims 1-9, 11, and 14-19 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. et al., in view of Juan et al..

None of Tang et al. and Juan et al. teaches adeno-associated virus as a vector recited in claim 10.

Nicklin et al. et al teaches that advances in vector targeting strategies have been rapid within the field of DNA-based viruses, particularly adenovirus (Ad) and more recently adeno-associated virus (AAV) based vectors, and both Ad and AAV vectors can be modified in tropism for gene therapy purpose.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to integrate the teachings of Nicklin et al., regarding use of adeno-associated virus (AAV) based vectors in gene therapy with the combined teachings of Tang et al. and Juan et al. regarding expressing a therapeutic gene from an adenoviral vector, by substituting adenoviral vector taught by Juan et al. with an adeno-associated vector taught by Nicklin et al. to arrive at the claim 10 of instant application.

One having ordinary skill in the art would have been motivated to integrate the teachings of Nicklin et al. with the combined teachings of Tang et al. and Juan et al. because Nicklin et al teaches that both adenovirus (Ad) and adeno-associated virus (AAV) based vectors can be modified in tropism for gene therapy purpose.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoplast cell line by the teachings of Tang et al., (ii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and (iii) demonstration of both adenovirus (Ad) and adeno-associated virus (AAV) based vectors can be modified in tropism for gene therapy purpose by the teachings of Nicklin et al. et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

4. Claims 12 and 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001), as applied to claims 1-9, 11, and 14-19 above, and further in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. *J Gene Med.* 3(3):240-51, 2001).

The teachings of Tang et al. and Juan et al. have been discussed in the preceding section of the rejection of claims 1-9, 11, and 14-19 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. et al., in view of Juan et al..

None of Tang et al. and Juan et al. teaches the genetically modified cell is a pluripotent or toipotent stem cell recited in claim 12, and the genetically modified cell is a mesenchymal stem cell (MSC) recited in claim 13.

Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types. Turgeman teaches that hMSCs represent a novel platform for skeletal gene therapy and that hMSCs can be genetically engineered to express desired therapeutic proteins inducing specific differentiation pathways (See abstract, page 240, Turgeman et al.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to integrate the teachings of Turgeman et al. regarding the use genetically engineered hMSCs for gene therapy to express desired therapeutic proteins, whereas the hMSCs can be directed to specific differentiation pathways, with the combined teachings of Tang et al. and Juan et al. regarding expressing a therapeutic gene from a vector to arrive at the claims 12 and 13 of instant application.

One having ordinary skill in the art would have been motivated to integrate the teachings of Turgeman et al. with the combined teachings of Tang et al. and Juan et al. because Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types and hMSCs can function as a transgene vehicle and can be genetically engineered to express desired therapeutic proteins and the genetically engineered hMSCs can be induced toward specific differentiation pathways for treatment.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoplast cell line by the teachings of Tang et al., (ii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and (iii) demonstration of genetically engineered human mesenchymal stem cells expressing human BMP-2 from an adenoviral vector leading to formation of cartilage and bone *in vivo* for treatment of osteoporesis by the teachings of Turgeman et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632